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on March 9, 2004

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03/09/04
Date of Signature

PATENT
#03-0164-UNI
Case #J7170(V)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Brading et al.
Serial No.: 10/719,137
Filed: November 21, 2003
For: COMPOSITION

Edgewater, New Jersey 07020
March 9, 2004

SUBMISSION OF PRIORITY DOCUMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Pursuant to rule 55(b) of the Rules of Practice in Patent Cases, Applicant(s) is/are submitting herewith a certified copy of the European Application No. 02258069.0 filed November 22, 2002, and European Application No. 03251046.3 filed February 21, 2003, upon which the claim for priority under 35 U.S.C. § 119 was made in the United States.

It is respectfully requested that the priority document be made part of the file history.

Respectfully submitted,

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Europäisches Patentamt	European Patent Office	Office européen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

02258069.0

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 02258069.0
Demande no:

Anmeldetag:
Date of filing: 22.11.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

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GRANDE BRETAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Composition

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

A61K7/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

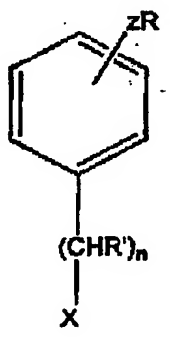
COMPOSITION

The present invention relates to an oral composition comprising a halogenated hydroxydiphenyl ether and a delivery enhancing agent.

Alkyl hydroxybenzoates (parabens) are known in the art where the alkyl group is methyl. For example, methyl hydroxybenzoate is mentioned, albeit fleetingly, for use in medicinal and oral care preparations as a preservative (WO 00/09507 and WO 00/69401).

We have found that there exists a range of compounds which improve the delivery of halogenated bisphenolic compounds such as triclosan.

Accordingly the present invention provides an oral composition comprising from 0.1 to 3.5% by weight of the composition of a compound of Formula 1:



Formula (1)

wherein:

z takes a value of from 1 to 5 and the R groups are independently selected from the group consisting of: H, F, Cl, Br, -OH, C_1-C_5 alkyl, -C(O)H, and -C(O)-C_1-C_{15} alkyl;

R' is selected from the group consisting of: H, -OH, F, Cl, Br, I, and C_1-C_6 alkyl and n is an integer in the range from 0 to 12, preferably from 0 to 3; especially 0 or 1 and most preferably 0;

wherein X is a group selected from -C(O)-NH-R'', -R'', -C(O-R'',-C(O)O-R'', and $-SO_2$-R'', and R'' is selected from the group consisting of: $-C_{1-16}$ alkyl, $-CH_2C_6H_6$, and wherein the composition additionally comprises a halogenated hydroxydiphenyl ether at from 0.01 to 0.4% by weight of the composition.

In a preferred embodiment X is-C(O)O-R'', wherein R'' is a substituted or unsubstituted branched or straight chain hydrocarbon moiety.

Preferably R'' is an aliphatic alkyl group, more preferably comprising from 1 to 16 and especially from 3 to 12 carbon atoms. Examples of suitable R'' groups include methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, benzyl, heptyl, octyl, 2-ethyl hexyl, nonyl, decyl, undecyl, dodecyl or tridecyl. Of these the most preferred are the straight chain alkyls. The most preferred compound is where R'' is n-octyl.

According to Formula 1 z ranges from 1 to 5 and is preferably 1 or 2, more preferably 1. It is preferred that at least one R group is in the para or meta position, more preferably the para position.

According to Formula 1 R' is selected from the group consisting of: H, -OH, F, Cl, Br, I, and C1-C6 alkyl.

Manufacture of such compounds as represented by Formula 1 would be a simple step for the man skilled in the art to carry out.

The most preferred compound is n-octyl parahydroxy benzoate.

The compound according to Formula 1 is preferably present at from 0.1 to 3.5% by weight of the composition. Preferably, in an amount ranging from 0.15 to 2.3% by weight and most preferably from 0.2 to 1.3% by weight of the composition.

The composition according to the invention also comprises a halogenated hydroxydiphenyl ether compound, more preferably 2', 4, 4'-trichloro-2-hydroxy-diphenyl ether, hereinafter known as triclosan. Preferably the halogenated hydroxydiphenyl ether is present at from 0.01 to 0.4% by weight of the composition.

The composition according to the invention may also comprise a divalent metal salt. Preferably, the divalent metal salt is a salt selected from the group consisting of zinc- and stannous salts such as zinc citrate, zinc sulphate, zinc glycinate, sodium zinc citrate, stannous pyrophosphate and

mixtures thereof. The preferable divalent metal salt is zinc citrate.

Suitably, the amount of divalent metal salt ranges from 0.01 to 10% by weight of the composition, preferably from 0.05 to 5% by weight, more preferably from 0.1 to 2% by weight and especially preferably from 0.3 to 0.9% by weight of the composition.

The oral composition according to the invention comprise further ingredients which are common in the art, such as:

antimicrobial agents, e.g. chlorhexidine, sanguinarine extract, metronidazole, quaternary ammonium compounds, such as cetylpyridinium chloride; bis-guanides, such as chlorhexidine digluconate, hexetidine, octenidine, alexidine; and halogenated bisphenolic compounds, such as 2,2' methylenebis-(4-chloro-6-bromophenol);

anti-inflammatory agents such as ibuprofen, flurbiprofen, aspirin, indomethacin etc.;

anti-caries agents such as sodium- and stannous fluoride, aminefluorides, sodium monofluorophosphate, sodium trimeta phosphate and casein;

plaque buffers such as urea, calcium lactate, calcium glycerophosphate and strontium polyacrylates;

vitamins such as Vitamins A, C and E;

plant extracts;

desensitising agents, e.g. potassium citrate, potassium chloride, potassium tartrate, potassium bicarbonate, potassium oxalate, potassium nitrate and strontium salts;

anti-calculus agents, e.g. alkali-metal pyrophosphates, hypophosphite-containing polymers, organic phosphonates and phosphocitrates etc.;

biomolecules, e.g. bacteriocins, antibodies, enzymes, etc.;

flavours, e.g. peppermint and spearmint oils;

proteinaceous materials such as collagen;

preservatives;

opacifying agents;

colouring agents;

pH-adjusting agents;

sweetening agents;

pharmaceutically acceptable carriers, e.g. starch, sucrose, water or water/alcohol systems etc.;

surfactants, such as anionic, nonionic, cationic and zwitterionic or amphoteric surfactants;

particulate abrasive materials such as silicas, aluminas, calcium carbonates, dicalciumphosphates, calcium pyrophosphates, hydroxyapatites, trimetaphosphates, insoluble hexametaphosphates and so on, including agglomerated particulate abrasive materials, usually in amounts between 3 and 60% by weight of the oral care composition. Preferred abrasives are chalk and silica, more preferably fine ground natural chalk.

Humectants such as glycerol, sorbitol, propyleneglycol, xylitol, lactitol etc.;

binders and thickeners such as sodium carboxymethyl-cellulose, hydroxyethyl cellulose (Natrosol®), xanthan gum, gum arabic etc. as well as synthetic polymers such as polyacrylates and carboxyvinyl polymers such as Carbopol®;

polymeric compounds which can enhance the delivery of active ingredients such as antimicrobial agents can also be included;

buffers and salts to buffer the pH and ionic strength of the oral care composition; and

other optional ingredients that may be included are e.g. bleaching agents such as peroxy compounds e.g. potassium peroxydiphosphate, effervescing systems such as sodium bicarbonate/citric acid systems, colour change systems, and so on.

Liposomes may also be used to improve delivery or stability of active ingredients.

The oral compositions may be in any form common in the art, e.g. toothpaste, gel, mousse, aerosol, gum, lozenge, powder, cream, etc. and may also be formulated into systems for use in dual-compartment type dispensers.

Embodiments according to the invention shall now be discussed with reference to the following non-limiting examples.

EXAMPLE 1

The following is a formulation according to the present invention. It is made by known processes.

Ingredient	%w/w
70% aq.sorbitol	45.0
Saccharin	0.2
Polyethylene glycol	2.0
Titanium dioxide	1.0
Sodium fluoride	0.32
Thickening silica	9.0
Abrasive silica	10.0
Sodium lauryl sulphate	1.6
Sodium carboxymethylcellulose	0.8
Flavour	1.0
Zinc citrate trihydrate	0.75
n-Octyl paraben	1.0
Triclosan	0.2
Water	to 100

EXAMPLE 2

Toothpaste formulations (minus the abrasives) comprising 0.2% w/w triclosan and varying levels of n-octyl paraben were tested in a salivary sediment model similar to that described by R.L. Wijeijweera and I. Kleinberg in Archs. Oral Biol., Vol. 34, No. 1, 1989, pages 43-53, using ex-vivo samples and measuring the amount of triclosan delivered to the salivary sediment.

The values represent the amount (ppm per ml sediment suspension) of triclosan delivered.

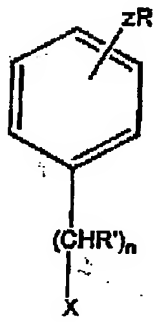
Table 1

5(w/w) n-octyl paraben	TCN delivered
0	7.4
0.4	9.8
0.6	10.3
0.8	11.6

As can be clearly seen the n-octyl paraben increases the level of triclosan delivered. This is an unexpected effect.

CLAIMS

1. An oral composition comprising from 0.1 to 3.5% by weight of the composition of a compound of Formula 1:



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R' is selected from the group consisting of: H, -OH, F, Cl, Br, I, and C_1-C_6 alkyl and n is an integer in the range from 0 to 12;

wherein X is a group selected from -C(O)-NH-R'', -R'', -C(O-R'',-C(O)O-R'', and $-SO_2$-R'', and R'' is selected from the group consisting of: -C_{1-16}-alkyl, -$CH_2C_6H_5$, and wherein the composition additionally comprises a halogenated hydroxydiphenyl ether at from 0.01 to 0.4% by weight of the composition.

2. An oral composition according to claim 1, wherein X is-C(O)O-R''.

3. An oral composition according to claim 1 or 2, wherein R'' is an aliphatic alkyl group.

4. An oral composition according to any preceding claim, wherein R'' represents a straight chain alkyl group comprising from 5 to 12 carbon atoms.

5. An oral composition according to any preceding claim, wherein -R'' is C6-C12 alkyl.

6. An oral composition according to any preceding claim, wherein -R'' is C8 alkyl.

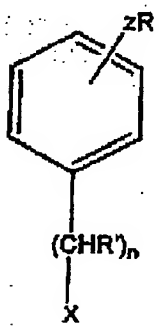
7. An oral composition according to any preceding claim, wherein z is 1.

8. An oral composition according to any preceding claim, wherein the halogenated hydroxydiphenyl ether is triclosan.

9. Oral composition according to any preceding claim wherein the composition comprises an agent selected from the group consisting of anti-caries agents, anti-tartar agents, anti-oral malodour agents, tooth whitening agents, breath freshening agents and mixtures thereof.

ABSTRACT

An oral composition comprising from 0.1 to 3.5% by weight of the composition of a compound of Formula 1:



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wherein X is a group selected from -C(O)-NH-R'', -R'', -C(O-R'',-C(O)O-R'', and $-SO_2$-R'', and R'' is selected from the group consisting of: $-C_{1-16}$-alkyl, $-CH_2C_6H_6$, and wherein the composition additionally comprises a halogenated hydroxydiphenyl ether at from 0.01 to 0.4% by weight of the composition.